PATENT
Attorney Docket No. 468972-00006/A-67412/RFT/RMS/RMK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

MEADE *et al.*

Serial No.: 09/192,167

Filed: November 13, 1998

For: *METHODS OF MAKING MODIFIED NUCLEOSIDES*

Group No. 1623

Examiner: L. E. Crane

CERTIFICATE OF MAILING

I hereby certify that this correspondence, including listed enclosures, is being deposited with the Untied States Postal Service as First Class Mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on :

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Jere Valles

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Thomas J. Meade, do hereby declare as follows:

1. I received a Ph.D. degree in Inorganic Chemistry in 1985 from The Ohio State University. I currently hold a triple appointment as a Professor Of Chemistry; Biochemistry and Molecular and Cell Biology; and Neurobiology and Physiology at Northwestern University. Prior to this, I was a Senior Research Faculty in the Division of Biology and the Beckman Institute, at the California Institute of Technology.

2. Attached to this Declaration as Exhibit 1 is a copy of my curriculum vitae and a list of publications.

3. I am on the Scientific Advisory Board and a consultant for Clinic Micro Sensors, the exclusive licensee of this patent application.

4. I have read and I understand the above-identified patent application, the and the Office Action mailed May 30, 2002. In addition, I would like to thank the Examiner for granting the informative and useful interview that took place on October 17, 2002.

5. As discussed in the interview, it is my opinion that the term "cyclization agent" as used in the context of the specification, e.g. in connection with the synthesis of modified nucleosides, would be understood by those of skill in the art to be a catalytic agent, such as DBO, DBU, DISN, BrCN, or heat, that could effect the cyclization of anydronucleosides.

6. Similarly, it is my opinion that the term "cyclized intermediate" as used the context of the specification, e.g. in connection with the synthesis of modified nucleosides, would be understood by those of skill in the art to be bicyclic or cyclic nucleoside derivatives such as 2'-deoxy-2'-alkoxyamino uridine derivatives, 2',3'-cyclic nucleotides, and oxazoline derivatives.

7. In support of these opinions, I note that there are a number of references (McGee, et al., (1996) Tetrahedron Letters, 37:1995-1998 (attached as Exhibit 9), Sebesta, et al. (1996) Tetrahedron, 52:14385-14402 (attached as Exhibit 10), McGee, et al. (1996) J. Org. Chem., 61:781-785 (attached as Exhibit 11), and Ferris and Yanagawa (1984) J. Org. Chem., 49:2121-2125 (attached as Exhibit 12)) that describe DBO, DBU, DISN, BrCN, and heat as agents that effect the cyclization of anhydronucleosides, as well

as cyclized intermediates such as 2'-deoxy-2'-alkoxyamino uridine derivatives, 2',3'-cyclic nucleotides, and oxazoline derivatives (*See* Exhibits 9, 10, 11 and 12).

8. It is my opinion that oligonucleotide synthesis using phosphoramidite chemistry is well established and has been for a number of years. The basic method for synthesizing oligonucleotides using phosphoramidite chemistry involves a series of deprotection, coupling, capping, and oxidation steps that are repeated until the specified nucleotide chain is constructed.

9. These methods are outlined in standard reference books such as Gait, M., ed. (1984) *Oligonucleotide Synthesis: A Practical Approach*, Oxford University Press, Oxford, and Eckstein, F., ed. (1991) *Oligonucleotides and Analogues: A Practical Approach*, Oxford University Press, Oxford. Additionally, descriptions of oligonucleotide synthesis using phosphoramidite chemistry can be found in Meade and Kayyem (1995) Angew. Chem. Int. Ed. Engl. 34:352-353 (attached as Exhibit 13), Yu et al. (2001) J. Org. Chem., 66:2937-2942 (attached as Exhibit 14); Krider, et al. (2001) Inorg. Chem., 40:4002-4009 (attached as Exhibit 6); Krider et al. (2002) Bioconjugate Chem., 13:155-162 (attached as Exhibit 5); Frank and Meade (2003) Inorg. Chem. 42:1039-1044 (attached as Exhibit 8) and Anne, et al. (2001) Bioconjugate Chem., 12:396-405 (attached as Exhibit 15). Accordingly, it is my opinion that those of skill in the art would clearly understand how to add a phosphoramidite group to a modified nucleoside.

10. It is my opinion that the term "polydentate ligand" would be understood by those of skill in the art to refer to a ligand that is attached to a central metal ion by bonds from two or more donor atoms. Ligands with suitable donor atoms include ligands

such as P_2N_2, bipyridine, and the like, that use nitrogen, oxygen, etc. as donor atoms. Bianchini, et al. (1990) J. Am. Chem. Soc., 122:9190-9197 (attached as Exhibit 18); Klink et al. (2002) J. Phys. Chem., 106:3681-3689 (attached as Exhibit 19); and Browne, et al. (2001) J. Chem. Soc., Dalton Trans., 2001:3513-3519 (attached as Exhibit 20) describe polydentate ligands, using this term, as ligands attached to a central metal ion by bonds from two or more donor atoms.

11. It is my opinion that the term "anhydronucleoside" would be understood by those of skill in the art to refer to pyrimidine nucleosides comprising an oxygen bridge between the C-2 of the base pyrimidine and C-2' or C-3' of the ribose or purine nuclosides that have an oxygen bridge between the C-8 of the purine residue and a hydroxyl group, e.g., C-2' or C-3' of the ribose. Ferris and Yanagawa (1984) J. Org. Chem., 49:2121-2125 (attached as Exhibit 12); David and de Sennyey (1982) J. Chem. Soc., Perkin Trans. 1, 2:385-93 5 (attached as Exhibit 16); Qiu, et al., (1998) Angewandte Chemie, International Edition, 37:1440-415 (attached as Exhibit 17); Mizuno and Sasaki (1965) Tetrahedron Lett., 50:4579-4584 (attached as Exhibit 21); Robins and Kanai (1976) J. Org. Chem., 41: 1886-1887 (attached as Exhibit 22); and Kaneko et al. (1978) Nucleic Acid Chemistry, 595-599 (attached as Exhibit 23); and Jung, et al. (1998) Nucleosides & Nucleotides, 17:2383-2387 (attached as Exhibit 24) use "anyhdro-nucleoside" to describe nucleosides having an oxygen bridge between the C-2 of the base pyrimidine and C-2' or C-3' of the ribose or purine nuclosides that have an oxygen bridge between the C-8 of the purine residue and C-2' or C-3' of the ribose.

12. All statements made herein of my own knowledge are true and all statements on information and belief are believed to be true. All statements made by me

herein are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code, and that any willful false statements may jeopardize the validity of any patent resulting therefrom.

Date: 5-8-03

Signed: _____

Thomas J. Meade